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Abstract

Levamisole was administered to 177 patients with gastrointestinal cancer (88 curative resection, 58 noncurative resection and 31 without resection). It was administered at a daily dose of 150 mg for three consecutive days every other week. The administration was started, as a rule, 3 days before operation. This medication was repeated as frequently as possible at least for one month. The cellular immunity and 18-month survival rate of treated and control groups were compared. Levamisole effectively improved peripheral lymphocyte blastformation against phytohemagglutinin and increased the numbers of peripheral blood lymphocytes. Levamisole caused extremely high blastformation rates, in general, enhanced PPD reactions in non-curative resection cases 7 months after operation and showed no influence upon the number of peripheral blood lymphocyte. The effect of levamisole on the 6-month survival rate was most marked in patients without resection. Increased 12-month survival rate was marked in non-curative resection cases and, to a lesser extent, curative resection cases. Patients without resection had a slightly improved 12-month survival rate. Levamisole improved the 18-month survival rate in resectable cases; however, there were no significant differences in 18-month survival between levamisole and control groups of patients not undergoing resection. The results suggest that levamisole is effective in the patients whose tumor cells have been decreased by any method.

KEYWORDS: levamisole. gastrointestinal cancer, cell-mediated immunity, survival rate

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IMMUNOTHERAPY OF GASTROINTESTINAL CANCER PATIENTS WITH LEVAMISOLE

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Abstract. Levamisole was administered to 177 patients with gastrointestinal cancer (88 curative resection, 58 noncurative resection and 31 without resection). It was administered at a daily dose of 150 mg for three consecutive days every other week. The administration was started, as a rule, 3 days before operation. This medication was repeated as frequently as possible at least for one month. The cellular immunity and 18-month survival rate of treated and control groups were compared. Levamisole effectively improved peripheral lymphocyte blastformation against phytohemagglutinin and increased the numbers of peripheral blood lymphocytes. Levamisole caused extremely high blastformation rates, in general, enhanced PPD reactions in noncurative resection cases 7 months after operation and showed no influence upon the number of peripheral blood lymphocyte. The effect of levamisole on the 6-month survival rate was most marked in patients without resection. Increased 12-month survival rate was marked in noncurative resection cases and, to a lesser extent, curative resection cases. Patients without resection had a slightly improved 12-month survival rate. Levamisole improved the 18-month survival rate in resectable cases; however, there were no significant differences in 18-month survival between levamisole and control groups of patients not undergoing resection. The results suggest that levamisole is effective in the patients whose tumor cells have been decreased by any method.

Key words: levamisole, gastrointestinal cancer, cell-mediated immunity, survival rate

It is more than 10 years since immunotherapy was introduced as a treatment of cancer in addition to surgical therapy, radiotherapy and chemotherapy. Rapid advances in the study of immunostimulators have taken place since 1969 when bacille Calmette Guérin (BCG) was first described as a promising aid to cancer therapy (1) and various immunostimulators have been put to practical use. The results have been generally encouraging (2).

In contrast to conventional immunostimulators of biological origin, levamisole is a purely chemical synthetic product (3). The published data on the ability of levamisole to enhance immunity and to increase survival have been collected and analysed by Symoens *et al.* (4). Our results have been given elsewhere (5).

This paper deals with 177 patients with gastrointestinal cancer who received levamisole in the schedule described in the previous report (5). We have drawn the conclusion from this study that levamisole is effective in improving the 18-month survival rate postoperatively in patients with gastrointestinal cancer.

MATERIALS AND METHODS

Of patients who were hospitalized in our Department of Surgery and underwent an operation for gastric or colorectal cancer, 241 received levamisole. Of these patients, 177 who were given levamisole for more than one month were admitted to the evaluation. Cancer was located in the esophagus in 7 patients, stomach in 99, large intestine in 48 and elsewhere in 23. Eighty-eight patients underwent curative resection, 58 noncurative resection and 31 were not resected. The control for this study was a group of 215 patients treated by non-immunotherapy (Table 1).

TABLE 1. PATIENTS RECEIVING LEVAMISOLE FOR ONE MONTH OR MORE

Site of cancer	Curative resection	Noncurative resection	Without resection	Total
Esophagus	2	0	5	7
Stomach	57	35	7	99
Stage I	19	0	0	19
II	13	0	0	13
III	18	11	0	29
IV	7	24	7	38
Colorectum	26	14	8	48
Other	3	9	11	23
Total	88	58	31	177
Control	122	62	31	215

There was no difference between control and levamisole groups in regard to patients' age, surgical intervention or anticancer therapy. Courses of levamisole therapy each consisting of consecutive three-day administrations of a daily dose of 150 mg followed by an 11-day withdrawal period were repeated as much as possible and for at least one month. As concomitant chemotherapy, mitomycin C was injected in a dose of 4 mg twice a week for 5 weeks and FT-207 was given orally in a daily dose ranging from 600 to 800 mg for long periods of time. Immunological parameters measured included the blastformation rate of peripheral blood lymphocytes against phytohemagglutinin (PHA), PPD reactions and peripheral blood lymphocyte counts. Blastformation tests were performed using the author's stndared technique (6). PPD reactions were read 48 h after intradermal injection of 0.1 ml of a standard preparation of tuberculin.

RESULTS

Blastformation rate. The response of peripheral blood lymphocytes to PHA in the control group (free of immunotherapy) is shown in Fig. 1-a. The mean blastformation rate was a little under 50% after curative resection and a little under 40% after noncurative resection. With the latter, the percentage

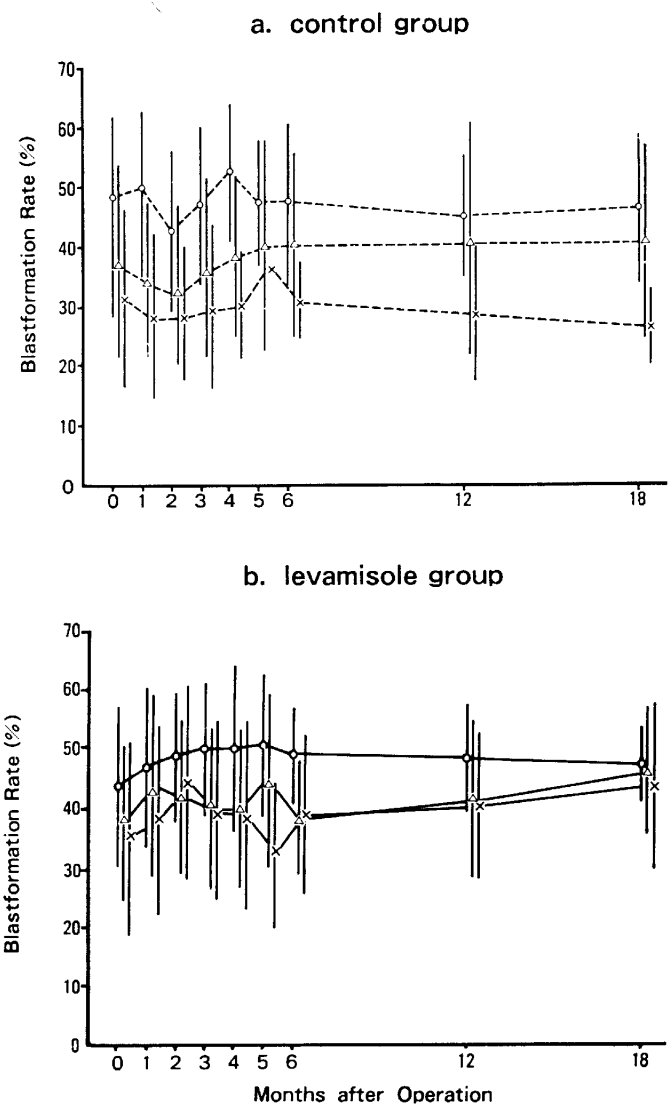

Fig. 1. Blastformation rate after operation.
○·····○, curative resection; △·····△, noncurative resection;
×·····×, with resection.

more or less diminished with time. The groups undergoing operation showed blastformation rates of the order of the preoperative level throughout the 18 months following resection.

Fig. 1-b shows the blastformation rates in the levamisole group during the 18-month postoperative period. In curative resection cases, the mean blastformation rate in the levamisole group was 44% before operation. This was lower than that of the control group. The rate rose to a level a little under 50% after operation. This was comparable to that of the control group. There was better variation in the rate throughout the postoperative 18 months. In noncurative resection cases, the blastformation rate was high from the first month after operation a mean greater than 40% until the 6th month. In the 12th and the 18th month, the blastformation rate rose further and approached that of curative resection cases. In cases without resection also, the blastformation rate tended to rise. The increase was similar to that observed in noncurative resection cases and was marked when compared with the blastformation rate in patients with neither resection nor immunotherapy.

A blastformation rate exceeding 40% is considered as indicative of the good condition of the patient (6). Fig. 2 compares the proportion of the patients with

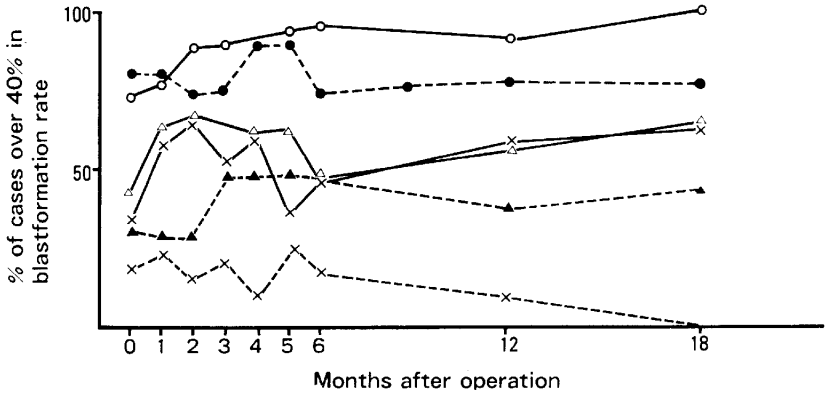

Fig. 2. Percent of cases over 40% in blastformation rate after operation.
——, levamisole group; ·····, control group; ○·····○, curative resection; △·····△, noncurative resection; ×·····×, without resection.

blastformation rates over 40% in levamisole and control groups. Regardless of whether the patients underwent resection or not, the proportion was always higher in the levamisole group. The difference increased with the duration of levamisole therapy. Setting the level of the blastformation rate at 40% rather than just the blastformation rate proved useful in the analysis of the effects of levamisole. This method correlated well with the results for survival described

below.

To ascertain whether levamisole was able to activate depressed cellular immunity, change in the blastformation rate with levamisole was followed in patients whose blastformation rate had been less than 40% before administration of levamisole and/or before operation. The percentage rose in most patients undergoing operation. In some patients without resection, the rate fell below the initial value after 12 to 16 weeks although it was high in the early stage of administration (Fig. 3). We roported previously that blastformation rates under

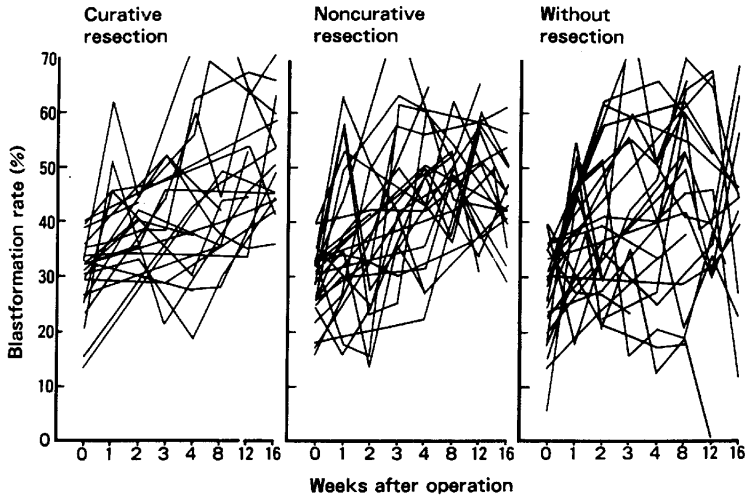

Fig. 3. Effect of levamisole on the cases of the blastformation rate under 40% before operation.

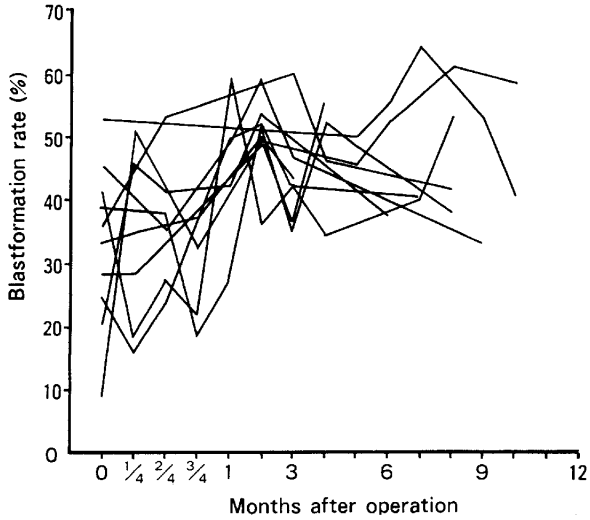

Fig. 4. Blastformation rate after operation in levamisole group. (>70 years old, curative resection)

40% were frequent in patients over 70 years old who underwent curative resection for cancer (7). As Fig. 4 shows, levamisole activated the blastformation rate markedly in aged patients undergoing curative resection for gastrointestinal cancer.

Peripheral blood lymphocyte count. Peripheral blood lymphocyte counts after 2 to 6 months of administration were different for each of the curative, noncura-

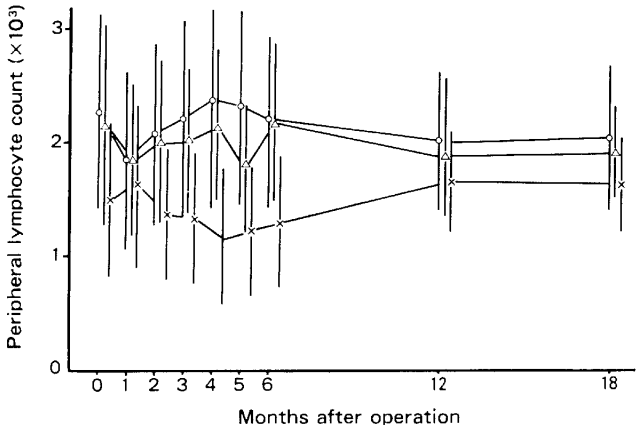

Fig. 5. Peripheral blood lymphocyte count after operation in levamisole group. ○——○, curative resection; △——△, noncurative resection, ×——×, without resection.

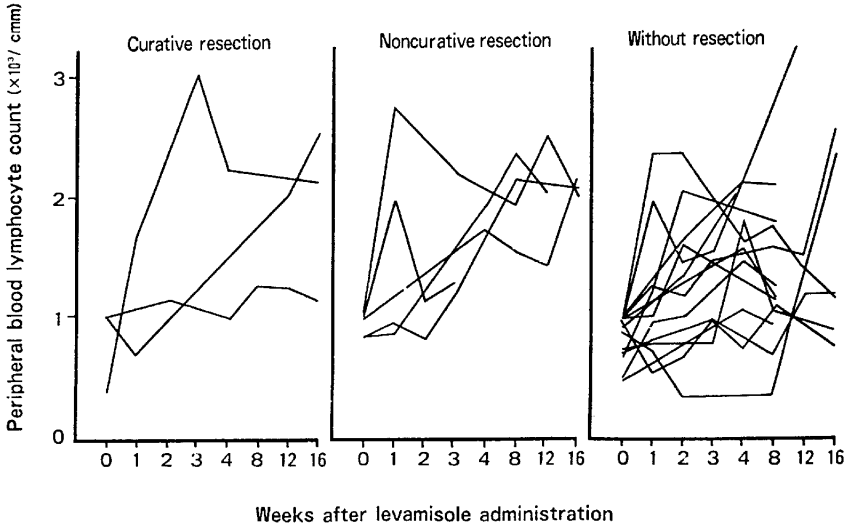

Fig. 6. Effect of levamisole on the cases of the peripheral blood lymphocyte count under 10^3/cmm.

tive resection, and nonresected groups. But in all three groups the counts had returned to the initial levels after 12 and 18 months. This indicated the lack of effect of levamisole on peripheral lymphocytes (Fig. 5). In most patients with lymphocyte counts below $1000/mm^3$ levamisole increased peripheral blood lymphocytes in the early period of administration (Fig. 6).

PPD skin reactions. PPD reactions during levamisole administration are summarized in Fig. 7. The upper part of the figure shows the major axis of the erythema up to 18 postoperative months. There were no marked differences among the three groups. The lower part of the figure shows the percentage of positive cases. The marked increase in positive cases between 7 and 18 months after the levamisole administration was characteristic.

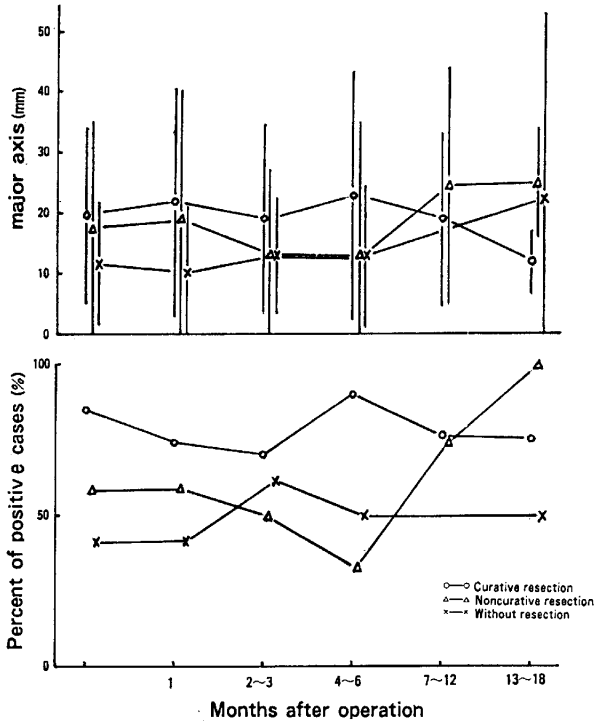

Fig. 7. PPD skin reaction after operation in levamisole group.

Clinical results. Monthly survival data from the patients with gastrointestinal cancer who received levamisole for one month or more and whose postoperative prognosis were monitored are given in Fig. 8, where dotted lines represent the control and solid lines represent the levamisole-treated groups. The survival rate was higher in the levamisole group than in the control group whether the patients underwent curative resection or noncurative resection or underwent

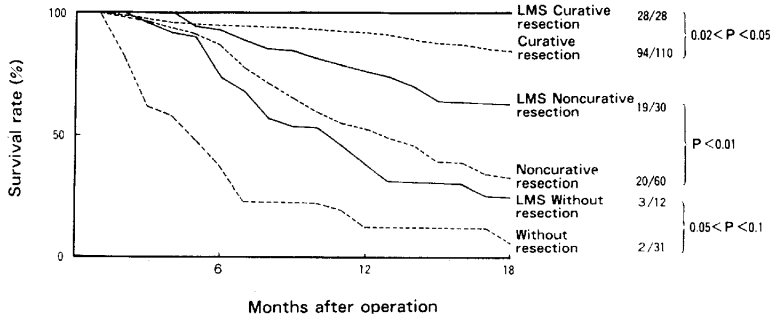

Fig. 8. Survival curves up to 18 months after operation for gastrointestinal cancer. ——, levamisole group; ·····, control group; LMS, levamisole.

without resection. This difference in survivals increased with time in patients undergoing resection. In patients without resection, it reached a maximum in the 7th month and decreased thereafter (Fig. 8).

Table 2 contrasts the 6-, 12- and 18-month survival rates of treated patients with those of controls. The x^2 test was used to test the level of significance. The difference in 6-month survival between levamisole and control groups was almost significant after noncurative resection; the difference was largest in patients without resection. The 12-month survival rate in noncurative resection

TABLE 2. SURVIVAL RATES FOR GASTROINTESTINAL CANCER

a. 6-month survival rate

Curability for operation	Control		LMS		x^2 test
	No.	%	No.	%	
Curative resection	116/122	95.1	71/71	100.0	$x^2=3.60$ $p<0.1$
Noncurative resection	54/62	87.1	43/46	93.5	$x^2=1.18$ $p<0.5$
Without resection	12/31	38.7	14/19	73.7	$x^2=5.77$ $0.01<p<0.02$

b. 12-month survival rate

Curability for operation	Control		LMS		x^2 test
	No.	%	No.	%	
Curative resection	112/122	92.6	44/44	100.0	$x^2=3.83$ $p=0.05$
Noncurative resection	33/62	53.2	26/34	76.5	$x^2=5.01$ $0.02<p<0.05$
Without resection	4/31	12.9	5/13	38.5	$x^2=3.68$ $p=0.05$

c. 18-month survival rate

Curability for operation	Control		LMS		χ^2 test
	No.	%	No.	%	
Curative operation	94/110	85.5	28/28	100.0	$\chi^2=4.61$ $0.02<p<0.05$
Noncurative resection	20/60	33.3	19/30	63.3	$\chi^2=7.33$ $p<0.01$
Without resection	2/31	6.5	3/12	25.0	$\chi^2=2.90$ $0.05<p<0.1$

LMS: levamisole

cases showed the biggest response to levamisole therapy. In the 18th month, prolongation of survival due to levamisole was statiscally significant in curative resection cases. In patients without resection there was no significant difference in survival between levamisole and control groups.

Side effects. Oral levamisole administration was accompanied by gastrointestinal, central nervous system, dermatological and hematological side effects. Gastrointestinal symtoms were possibly due in part to operative disturbance since the administration of levamisole to patients with gastrointestinal cancer was commenced just before operation. The overall incidence was low. Of 200 patients who received levamisole, 5 showed gastrointestinal symptoms (2 nausea, 2 abdominal pain and diarrhea); 8 showed central nervous symptoms (2 headache, 2 excitement, 1 depression and 3 fever); 5 showed eruptions. The incidence was showed for all side effects. Symptoms other than eruptions did not occur during withdrawal pariods. These adverse reactions (eruptions included)

TABLE 3. SIDE-EFFECTS OF LEVAMISOLE (200 PATIENTS TAEATED)

Type of side effects	No. of patients	No. of stopped
Gastrointestinal complaints	5	2
Nausea	2	0
Abdominal pain	2	2
Diarrhea	1	0
CNS-stimulation	8	1
Headache	2	1
Irritability	2	0
Sensory depression	1	0
Fever	3	0
Skin rash		
Skin rash, urticaria	5	3
Blood		
Granulocytopenia	1	1
Total	19 (9.5%)	7 (3.5%)

subsided rapidly upon cessation of therapy regardless of their severity. Therapy was discontinued in some patients because of gastrointestinal symptoms (2 cases), central nervous symptoms (1 cases) or eruptions (3 cases). Granulocytopenia, a hematological toxic effect of levamisole, occurred in one patient but recovered with cessation of therapy. The overall incidence of side effects was 9.5% (19 of 200 patients). Side effects necessitating cessation of therapy occurred in 3.5% (7 of 200 patients) (Table 3).

DISCUSSION

It was in 1971 that Renoux, G. and Renoux, M. (8) first reported the ability of levamisole to enhance immune competence. Since then, extensive studies regarding the application of levamisole to cancer immunotherapy have been performed in Europe and the United States. The antitumor effects of levamisole are due to the fact that this drug activates and normalizes immune competence of the cancer-bearing body and that, secondarily it enhances resistance of the cancer-bearing body against tumor. Levamisole has no effect unless the immunity of the cancer-bearing body is impaired by the growth of cancer (9).

Many authors suggest that levamisole is particularly effective in improving depressed cellular immunity. According to *in vitro* studies, there is an increased response of peripheral blood lymphocytes to various mitogens in the early stage of levamisole therapy and this is maintained at high levels by sustained therapy (10). This is consitent with what we have reported previously (11). In our studies, blastformation rates which were low before therapy increased markedly in most patients after administration for one week. Surgical intervention is usually accompanied by impaired lymphocytes transformation lasting postoperatively for three weeks. Levamisole, if commenced before operation, prevented such postoperative depression in the blastformation rate. Our finding that the blastformation rate was far higher in the levamisole group than in the control group during the postoperative 18 months is further evidence of the immunostimulating property of this drug. The balstformation rate correlated well with the survival rate. Similar observations have been made by Renoux *et al.* (12). According to our unpublished data the responsiveness to PHA and T-cell mitogens such as Con A and PWM is enhanced by levamisole, but there is almost no increase in the response to LPS.

Ramot *et al.* (9) reported that levamisole increased T-cells in malignant disease. According to our unpublished data, in patients not receiving levamisole, both T-cells and active T-cells decreased following surgical intervention, reached a low in the second postoperative week, and recovered to their preoperative levels in or after the third week. By contrast, patients treated with levamisole did not show this postoperative decrease and T-cells were maintained at high levels for a

long time in parallel with patients' survival curves.

Many authors have reported that levamisole enhances skin reactions of cancer patients to PPD, DNCB, SK-SD and Candida (13–16), and some of them have postulated a relationship between enhancing skin reactions and prolonged survival (14). In this study, levamisole enhanced PPD reactions occurred in the noncurative resection cases after 7 months of administration only.

Contradiction exsists among workers concerning the influence of levamisole upon the peripheral blood lymphocyte count: some note elevation in the count (14) and others report elevation not in the count but in the proportion of active T-lymphocytes (9). On the whole, we did not find any fluctuation in lymphocyte counts during levamisole therapy, except for an increase occurring in patients whose lymphocytes had been markedly decreased before therapy.

Many publications refer to the antitumor activity of levamisole in animals (4) but the opinions are varied: levamisole by itself is effective; it is effective only when it is used in combination with anticancer agents, or it is ineffective. The effectiveness of levamisole was confirmed by Renoux *et al.* (17) who tested this drug against Lewis lung (3LL) tumor, and by our results for C3H/He mice bearing spontaneous mamary cancer and hepatoma MH 134 (18). Our subsequent results for hepatoma MH 134 (19) were in agreement with Doller *et al.* (20) in that levamisole was ineffective against transplanted tumor cells if the onset of administration was delayed for long. In combination with chemotherapy, Chirigos *et al.* (21) obtained remission of leukemia by the administration of BCNU and prevented recurrence for a long time by continued administration of levamisole. Potter *et al.* (22) disputed the effectiveness of levamisole.

The effects of levamisole against human cancer are not well documented. Those who considered levamisole effective against tumor include Amery *et al.* (23) who administered levamisole 150 mg/day to patients with operable bronchogenic cancer for three consecutive days evry other week from three days before operation (a course of 3-day medication and 11-day withdrawal); Rojas *et al.* (24) who used levamisole on the same dose schedule as Amery in patients who had received radiotherapy for inoperable Stage III breast cancer; Debois (25) who combined levamisole on the same schedule with radiotherapy for treatment of breast cancer, cephalocervical cancer and lung cancer; Renoux *et al.* (12) who administered levamisole to patients with advanced cancer beyond the control of available therapy; and we ourselves who used levamisole in the treatment of gastrointestinal cancer. Amery *et al.* (23), among others, interestingly showed that the larger tumors resected were, the more marked the antitumor activity of levamisole was. This agrees with our results for animal (18) and clinical studies (5). At the same time, they expressed doubts as to the dosage of levamisole, saying that good responses were obtained in patients weighing 70 Kg or less.

Debois *et al.*, analyzing their results for a 25-month follow-up study, remarked that, for breast cancer patients receiving levamisole, the difference in survival between levamisole and control groups increased in advanced stages of the disease. This agrees with our results for gastrointestinal cancer patients (5). In this study admitting only gastrointestinal cancer patients, significant increase in the 18-month survival rate due to levamisole was limited to Stage IV patients. In patients without resection, significant increase in the survival rate of the levamisole-treated group over control group lasted only one year and there was no difference 18 months later. Levamisole may, therefore, be most effective against tumor cells that are reduced in number (reduction therapy). In our previous experiment with mice bearing hepatoma MH 134, levamisole administered 10 or 14 days after tumor transplantation was very effective, whereas there was no difference between the treated and the control groups when administration had been started any later than that (19). Animal data from Symoens *et al.* (4) and Amery *et al.* (26) appear to support this hypothesis.

The incidence of clinical side effects of levamisole was around 9% and symptoms subsided quickly upon cessation of therapy. An increase in lymphocyte rate in the absence of leukopenia does not always lead to agranulocytosis as a side effect of levamisole. Gastrointestinal symptoms and psychogenic adverse reactions do not seem to interefere with long-term therapty, if they are relieved by appropriate measures such as intimate contact with patients, dosage adjustment or cessation of administration.

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